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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with dimethylphenols. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary reflecting limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to October, 1985. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

> U.S. EPA. 1980a. Ambient Water Quality Criteria Document for 2,4-Dimethylphenol. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA-440/5-80-044. NTIS PB81-117558.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e. protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities, and the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, any exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

The data available concerning the dimethylphenols are very limited. The only available reports are subchronic oral studies conducted in the Soviet Union (Maazik, 1967, 1968, 1970; Veldre and Janes, 1979). Using these limited data, the RfD_{SO} values are 0.42 mg/day for a 70 kg human for the 2,6-isomer and 0.98 mg/day for a 70 kg human for the 3,4-isomer. The RfD_O values are 0.042 mg/day and 0.098 mg/day for a 70 kg human for the 2,6-isomer and the 3,4-isomer, respectively. No data for the other isomers were located. Maximum CSs of 21 and 18.5 were calculated for the 2,6- and 3,4-isomers, respectively.

The RfD/RfD_S values derived in this document should only be used until more definitive toxicity and carcinogenicity studies of the dimethylphenols are available.

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LIST OF ABBREVIATIONS

CAS	Chemical Abstract Service
CS	Composite score
DMBA	Dimethyl benzanthracene
MED	Minimum effective dose
NOEL	No-observed-effect level
ppt	Parts per trillion
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RV_d	Dose-rating value
RV_e	Effect-rating value

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected physical properties and environmental fate of the dimethylphenols are listed in Table 1-1. The dimethylphenols can be classified as alkyl-substituted phenols. Based on their vapor pressures, dimethylphenols are expected to be mostly in the vapor phase and partly adsorbed onto particulate matter in the atmosphere. Both wet and dry deposition will remove some of the compound from air. Reaction with HO radical is expected to be the dominant removal mechanism in the normal atmosphere (HSDB, 1986). The atmospheric half-life of dimethylphenols listed in Table 1-1 is based on the HO radical reaction half-life of the isomeric cresols ranging from 3-6 hours (Atkinson, 1985) and the expectation that substitution of a second methyl group would increase the reaction rate even further than the rates with cresols. In polluted atmospheres, the reactions of nitrate radicals with the dimethylphenols are expected to be the fate determining processes. At a nitrate radical concentration of 355 ppt as found in an air pollution episode in the Los Angeles basin (Carter et al., 1981), the half-life of dimethylphenols that results from nitrate reactions is expected to be a few minutes. The two processes that are expected to be most significant in the removal of dimethylphenols from water are their reactions with peroxy radicals and biodegradation. Based on the estimated rate constant for 2,4-dimethylphenol reaction with peroxy radicals (Mabey et al., 1981), it is estimated that the dimethylphenol half-life is <1 day. Biodegradation was found to be significant in natural water by Visser et al. (1977) and Southworth et al. (1985), while Kaplin et al. (1968) reported that significant biodegradation of dimethylphenols is unlikely. Based on the biodegradation rate constant given by Mabey et al. (1981), it is estimated that the biodegradation half-lives of dimethylphenols in natural water will be ~3 days.

TABLE 1-1

Selected Physical and Chemical Properties and Half-Lives for Dimethylphenols

Property	Dimethylphenol Isomer						Reference
	2,3-	2,4-	2,5-	2,6-	3,4-	3,5-	
CAS number:	526-75-0	105-67-9	95-87-4	576-26-1	95-65-1	108-68-9	
Molecular weight:	122.16	122.16	122.16	122.16	122.16	1226.16	
Vapor pressure (20°C):	0.075 mm Hg	0.075 mm Hg	0.075 mm Hg	0.15 mm Hg	0.075 mm Hg	0.075 mm Hg	Weber et al., 1981
Water solubility (mg/L):	NA	7867 (23°C) 6474 (20°C)[a]	2050 (23°C)[b]	4404 (20°C)[a]	2876 (23°C)[b]	3627 (20°C)[a]	Banerjee et al., 1980; Rogers, 1982
pK_a	10.4	10.4; 10.6	10.3; 10.2	10.6	10.4	10.1	Fujita and Nakajima, 1969; Pearce and Simkins, 1968
Log octanol/water partition coefficient:	NA	2.30; 242; 2.50	2.33	2.36	2.23	2.35	Hansch and Leo, 1985; Westall et al., 1985; Garst and Wilson, 1984; Banerjee et al., 1980
Bioconcentration factor:	NA	150, bluegill sunfish (Lepomis macrochirus)	8-35 (estimated)	5-37 (estimated)	7-29 (estimated)	6-36 (estimated)	U.S. EPA, 1980a; Lyman et al., 1982
Soil adsorption coefficient:	NA	425-546 (estimated)	441 (estimated)	458 (estimated)	389 (estimated)	452 (estimated)	Lyman et al., 1982
Half-lives in:							
Air:	<6 hours	<6 hours	<6 hours	<6 hours	<6 hours	<6 hours	Carter et al., 1981; Atkinson, 1985
Water:	<1 day	<1 day	<1 day	<1 day	<1 day	<1 day	Mabey et al., 1981

[a]These are aqueous solubilities in the presence of 0.15 M NaCl.

[b]These are values estimated from the correlation equation of Banerjee et al. (1980) by using the K_{ow} values given in this table.

NA = Not available

Southworth et al. (1985) determined that the rate of removal of individual dimethylphenols was dependent upon microcosm exposure history and the presence of other phenol isomers. Adsorption onto suspended particles and sediments may become significant when iron oxide or organic carbon content of the particle in water are high (Artiola-Fortuny and Fuller, 1982). The two processes that may determine the fate of dimethylphenols in soil are biodegradation and sorption (Humenick et al., 1982). Biodegradation, however, was found to be insignificant in the soil from a creosote waste disposal site (Goerlitz et al., 1985). The toxicity of the other chemicals in the soil towards the microorganisms may be responsible for the observed lack of biodegradability at this site. The sorption of dimethylphenols in soil will increase as the organic carbon and iron oxide content of the soil increase (Artiola-Fortuny and Fuller, 1982; Isaacson and Sawhney, 1984). Dimethylphenols will not significantly leach from most soils, but low sorption in sandy aquifers may cause leaching into groundwater (Goerlitz et al., 1985). In the absence of significant biodegradation in such soils, as in tne case of the creosote waste disposal site (Goerlitz et al., 1985), leaching may become a significant process.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Miyamoto et al. (1969) orally dosed male Wistar rats with 35 mg/kg ^{14}C-3,4-dimethylphenol (labeled at 4-CH_3). Twenty-four hours after dosing, ~93.5% of the radioactivity was recovered from the urine, indicating extensive absorption from the gastrointestinal tract.

Pertinent data regarding the absorption of the other dimethylphenols following oral administration could not be located in the available literature.

2.2. INHALATION

Pertinent data regarding the absorption of dimethylphenols following inhalation exposure could not be located in the available literature.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

The limited information available regarding the toxic effects of dimethylphenols was taken from Russian studies with only limited details reported.

3.1. SUBCHRONIC

3.1.1. Oral. In a study by Maazik (1967), groups of 10 male albino rats were treated orally with 29.5 mg 2,6-dimethylphenol/kg/day or 72.5 mg 3,4-dimethylphenol/kg/day for 10 weeks. Another group of 10 rats (treatment unspecified) served as controls. Both treated groups of rats showed decreased body weights. When compared with controls, the 3,4-dimethylphenol-treated rats had increased relative weights of the spleen, heart, liver and lungs, while the 2,6-isomer-treated rats had increased relative liver and spleen weights. Histological examination showed marked atrophy and parenchymatous dystrophy of the liver cells in both treated groups. No significant changes were observed in hematological and clinical chemistry analyses. No other details of the study were provided.

In an experiment reported by Veldre and Janes (1979), 2,6- or 3,4-dimethylphenol was administered orally to white rats for 8 months. No toxic effects were observed at 0.6 mg 2,6-dimethylphenol/kg/day or 1.4 mg 3,4-dimethylphenol/kg/day. Decreased weight gain and changes in blood pressure and histopathological changes in internal organs (not otherwise specified) were observed in rats receiving 6 mg 2,6-dimethylphenol/kg/day and 14 mg 3,4-dimethylphenol/kg/day. No other details of the study were given.

Maazik (1967, 1968) reported the results of a study similar to the Veldre and Janes (1979) study; however, the low doses from the Veldre and Janes (1979) study of 0.6 and 1.4 mg/kg/day for the 2,6- and 3,4-isomers

were not used. A total of 53 rats were divided into groups (number/group unspecified), with one group of rats serving as a control. The treated rats were given oral doses of 2,6-dimethylphenol at 0.06 or 6 mg/kg/day or 3,4-dimethylphenol at 0.14 or 14 mg/kg/day for 8 months. No toxic effects were observed at the low doses of either isomer. At the high doses, growth rate and blood pressure were reduced compared with controls. Histological changes were observed in the liver, spleen, kidneys and heart of rats receiving both isomers and included fatty dystrophy and atrophy of hepatic cells, hyaline-droplet dystrophy in the kidneys, proliferation of myeloid and reticular cells, atrophy of the lymphoid follicles in the spleen and parenchymatous dystrophy of the heart cells. Further details of the study were not reported.

3.1.2. Inhalation. Pertinent data regarding the subchronic effects of dimethylphenols following inhalation exposure could not be located in the available literature.

3.2. CHRONIC

Pertinent data regarding the chronic effects of dimethylphenol following oral or inhalation exposure could not be located in the available literature.

3.3. TERATOGENIC AND OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the teratogenic and reproductive effects of dimethylphenols following oral or inhalation exposure could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

A study of the ability of 2,4-, 2,6-, 3,4- or 3,5-dimethylphenol to act as a promotor of skin tumors in mice (Boutwell and Bosch, 1959) is described in Section 4.3. Other pertinent data regarding interactions of dimethylphenol isomers could not be located in the available literature.

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data regarding the carcinogenicity of dimethylphenol to humans could not be located in the available literature.

4.2. BIOASSAYS

Pertinent data regarding the carcinogenicity of dimethylphenols in animals by either oral or inhalation routes of exposure could not be located in the available literature.

4.3. OTHER RELEVANT DATA

Boutwell and Bosch (1959) investigated the ability of several dimethylphenols to promote skin tumors in mice following a single initiating dose of DMBA and to act as whole carcinogens on the skin of mice. Groups of 30 female Sutter mice (2-3 months of age) were treated with a topical application of 75 µg DMBA in benzene, followed by 25 µl of 20% 2,4-, 2,6-, 3,4- or 3,5-dimethylphenol in benzene applied twice weekly to the back of each mouse for 15 weeks. Of the 30 mice in each group, 20-28 survived. Papillomas appeared rapidly in the treated groups, with the response almost identical to that (50%) recorded for mice when 0.5% croton oil (positive control) was used as the promotor. The highest response was with the 3,4-dimethylphenol application; 95% of the survivors had papillomas. 2,6-Dimethylphenol produced the lowest response, 30% compared with negative controls (no promotor or benzene solvent), where 13% of the mice had papillomas. At 15 weeks, 11% of the surviving 2,4-dimethylphenol-treated mice had carcinomas; at 23 weeks, this incidence increased to 18%. In 2,6-isomer-treated mice, 4% had carcinomas at 15 weeks and 11% had carcinomas at 23 weeks. No carcinomas were present at 15 weeks in mice treated with the 3,4- and 3,5-isomers; at 23 weeks, the incidences were 14 and 5%,

respectively. In the negative and croton oil controls, 0 and 4%, respectively, had carcinomas at 15 weeks, while 6 and 8%, respectively had carcinomas at 23 weeks. In this study, it appears that carcinomas developed earlier and at a higher incidence in dimethylphenol-treated mice inan in either negative or positive controls.

In a second experiment to compare the carcinogenicity of dimethylphenols with phenol in the one-stage mouse skin assay (Boutwell and Bosch, 1959), no initiator was used and 25 µl of 10% solutions of phenol or 2,4-, 2,5-, 3,4-, 3,5- or 2,6-dimethylphenol in benzene was applied weekly for 20 weeks. The incidences of papillomas ranged from 24-55% in the 2,4-, 2,5-, 3,4- and 3,5-isomer-treated groups. Mice treated with the 2,6-isomer showed the fewest treatment-related effects; 8% developed papillomas at 20 weeks, none developed carcinomas by 28 weeks. The 3,4- and 3,5-isomers showed the highest reponse: papillomas in 50 and 55%, respectively, and carcinomas in 4 and 5%, respectively. By week 28, carcinomas developed in 8-14% of the mice treated with the other isomers. Papillomas developed in 33% and carcinomas developed in 13% of the phenol-treated mice. The investigators concluded that 2,4-, 2,5- and 3,4-dimethylphenol were as carcinogenic as phenol in this test system, but that the 2,6-isomer was only weakly carcinogenic. Benzene (solvent) controls were not maintained.

All the dimethylphenol isomers have tested negative in reverse mutation assays with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 with and without metabolic activation (Pool and Lin, 1982; Florin et al., 1980). Szbalski (1958) also found 2,4-dimethylphenol to be negative in a reverse mutation assay with Escherichia coli strain Sd 4-73.

4.4. WEIGHT OF EVIDENCE

No oral or inhalation carcinogenicity studies of dimethylphenols have been reported. Data are available to suggest that the 2,4-, 2,5-, 3,4- and 3,5-dimethylphenols exhibit tumor-promoting activity and may act as whole carcinogens on mouse skin (Boutwell and Bosch, 1959).

Because limited evidence is available that dimethylphenols act as promotors or whole carcinogens on mouse skin (Boutwell and Bosch, 1959). According to the EPA classification (U.S. EPA, 1986), these compounds would be classified in category D, meaning that there is inadequate evidence to assess their human carcinogenic potential.

5. REGULATORY STANDARDS AND CRITERIA

No standards or criteria based on the health effects of dimethylphenols have been promulgated. The recommended ambient water quality criterion for 2,4-dimethylphenol, based on organoleptic data, is 400 µg/ℓ (U.S. EPA, 1980a).

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). The two reports (Maazik, 1968; Veldre and Janes, 1979) are available for oral risk assessment of 2,6- and 3,4-dimethylphenol. The study by Veldre and Janes (1979) provides NOELs 10-fold higher than those reported by Maazik (1968). Veldre and Janes (1979) administered 2,6- or 3,4-dimethylphenol orally to white rats for an 8-month period and reported no effects at 0.6 mg/kg 2,6-dimethylphenol or at 1.4 mg/kg 3,4-dimethylphenol. These doses are intermediate between the low and high doses administered by Maazik (1968). Effects on blood pressure, weight gain and histological changes in the liver, kidney and spleen were reported at the next higher doses (6 mg/kg 2,6-dimethylphenol and 14 mg/kg 3,4-dimethylphenol) by both Maazik (1968) and Veldre and Janes (1979).

Using the NOELs from Maazik (1968) and an uncertainty factor of 100, RfD_{SO} values of 0.0006 mg/kg/day (0.042 mg/day for a 70 kg human) for 2,6-dimethylphenol and 0.0014 mg/kg/day (0.098 mg/day for a 70 kg human) can be calculated. Using the NOELs from Veldre and Janes (1979), these values are 0.006 mg/kg/day (0.42 mg/day for a 70 kg human) for the 2,6-isomer and 0.014 mg/kg/day (0.98 mg/kg for a 70 kg human) for the 3,4-isomer. The NOELs from Veldre and Janes (1979) represent the highest NOELs below which no adverse effects were observed and are supported by the LOAELs and NOELs reported by Maazik (1968). Therefore, the RfD_{SO} values of 0.006 mg/kg/day (0.42 mg/day) for the 2,6-isomer and 0.014 mg/kg/day (0.98 mg/day) for the 3,4-isomer are recommended until more definitive toxicity and carcinogenicity data become available.

No data are available for the other dimethylphenol isomers; therefore, no RfD_{SO} values can be calculated.

6.1.2. Inhalation (RfD_{SI}). Pertinent data regarding the inhalation exposure of dimethylphenols could not be located in the available literature; therefore, RfD_{SI} values will not be derived.

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_O). For the purpose of this document, NOELs reported by Veldre and Janes (1979) will be used to calculate RfD_O values. Applying an additional uncertainty factor of 10 to the RfD_{SO} values in Section 6.1.1., RfD values are 0.0006 mg/kg/day or 0.042 mg/day for a 70 kg human for 2,6-dimethylphenol and 0.0014 mg/kg/day or 0.098 mg/day for a 70 kg human for 3,4-dimethylphenol. These values should be revised when more definitive toxicity and carcinogenicity data become available.

CSs for oral exposure to 2,6- and 3,4-dimethylphenol are listed in Table 6-1. These CSs are based on the studies of Maazik (1968, 1970) and Veldre and Janes (1979), which report changes in blood pressure and weight, and histopathological changes in the liver, kidneys and spleen. Maazik (1968, 1970) reported further details of the severity of the histopathological changes: fatty dystrophy and atrophy of hepatic cells, hyaline droplet dystrophy in the kidneys, atrophy of the lymphoid follicles in the spleen and parenchymatous dystrophy of heart cells. The lowest doses at which these effects were reported were 6 and 14 mg/kg/day for 2,6- and 3,4-dimethylphenol, respectively. Multiplying 6 and 15 mg/kg/day by the cube root of the ratio of the rat body weight (assumed to be 0.35 kg) to the reference human body weight (70 kg), and by 70 kg results in equivalent human doses of 71.8 and 167.6 mg/day, respectively. Because the study was subchronic, it is appropriate to divide the equivalent human doses by an uncertainty factor

TABLE 6-1

Oral Composite Scores for 2,6- and 3,4-Dimethylphenol[a]

Isomer	Species/ Strain	Sex	Exposure Dosage (mg/kg/day)	Human MED (mg/day)[b,c]	RV_e	Effect	RV_e	CS
2,6-Dimethylphenol	rat/albino	M	6	7.2	4.2	Weight loss, blood pressure increase, pathological changes in liver, kidney and spleen	5	21.0
3,4-Dimethylphenol	rat/albino	M	14	16.8	3.7	Weight loss, blood pressure increase, pathological changes in liver, kidney and spleen	5	18.5

[a]Source: Veldre and Janes, 1979; Maazik, 1968, 1970

[b]The human MED is calculated by multiplying the animal dose by the cube root of the ratio of the body weight of the experimental animal [note: 0.350 kg default value (U.S. EPA, 1980b)] to that of reference man [70 kg (U.S. EPA, 1970b)] and by 70 kg to express the result in mg/day.

[c]An uncertainty factor of 10 was applied to extrapolate from subchronic to chronic exposure.

of 10 resulting in chronic MEDs of 7.16 mg/day for 2,6-dimethylphenol and 16.76 mg/day for 3,4-dimethylphenol. The MEDs correspond to an RV_d of 4.2 for the 2,6-isomer and 3.7 for the 3,4-isomer. An RV_e of 5 was used based on the combined effect of histological changes in the liver, kidney and spleen and body weight changes. Multiplying the RV_d by the RV_e results in a CS of 21.0 for the 2,6-isomer and a CS of 18.5 for the 3,4-isomer.

No data were available for the other dimethylphenol isomers; RfD and CS values cannot be calculated.

6.2.2. Inhalation. Pertinent data regarding the toxicity of dimethylphenol isomers following inhalation exposure could not be located in the available literature.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. Pertinent data regarding the carcinogenic potential of dimethylphenol isomers following oral exposure could not be located in the available literature.

6.3.2. Inhalation. Pertinent data regarding the carcinogenic potential of dimethylphenol isomers following inhalation exposure could not be located in the available literature.

7. REFERENCES

Artiola-Fortuny, J. and W.H. Fuller. 1982. Adsorption of some monohydrobenzene derivatives by soils. Soil Sci. 133: 18-26.

Atkinson, R. 1985. Kinetics and mechanisms of the gas phase reactions of the hydroxyl radical with organic compounds under atmospheric conditions. Chem. Rev. 85: 191.

Banerjee, S., S.H. Yalkowsky and S.C. Valvani. 1980. Water solubility and octanol/water partition coefficients of organic limitations of the solubility partition coefficient correlation. Environ. Sci. Technol. 11: 1227-1229.

Boutwell, R.K. and P.K. Bosch. 1959. The tumor-promoting action of phenol and related compounds for mouse skin. Cancer Res. 19: 413-424.

Carter, W.P.L., A.M. Winer and J.N. Pitts, Jr. 1981. Major atmospheric sink for phenol and the cresols. Reaction with the nitrate radical. Environ. Sci. Technol. 15: 829-831.

Florin, I., L. Rutberg, M. Curvall and C.R. Enzell. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology. 15(3): 219-232.

Fujita, T. and M. Nakajima. 1969. The correlation between physiological activity and physicochemical property of the substituted phenols. Res. Rev. 25: 319-326.

Garst, J.E. and W.C. Wilson. 1984. Accurate, wide-range, automated, high-performance liquid chromatographic method for the estimation of octanol/water partition coefficients. I: Effect of chromatographic conditions and procedure variables on accuracy and reproducibility of the method. J. Pharmacol. Sci. 73(11): 1616-1623.

Goerlitz, D.F., D.E. Troutman, E.M. Godsy and B.J. Franks. 1985. Migration of wood-preserving chemicals in contaminated groundwater in a sand aquifer at Pensacola, FL. Environ. Sci. Technol. 19(10): 955-961.

Hansch, C. and A.J. Leo. 1985. Medchem Project. Issue No. 26. Pomona College, Claremont, CA.

HSDB. (Hazardous Substance Databank). 1986. NLM. Online: 1986.

Humenick, M.J., L.N. Britton and C.F. Mattox. 1982. Natural restoration of groundwater in UCG. In Situ. 6: 107-125.

Isaacson, P.J. and B.L. Sawhney. 1984. Measurement of vapor sorption: Influence of organic matter on clay sorption of 2,6-dimethylphenol. Soil Sci. 138(6): 436-439.

Kaplin, V.T., L.V. Semenchenko and E.G. Ivanov. 1968. Decomposition of a phenol mixture in natural waters (miniature-scale operation). Gidroknim Mater. 46: 199-202. (CA 69:69568h)

Lyman, W.J., W.F. Reehl and D.H. Rosenblatt. 1982. Handbook of Chemical Property Estimation Methods. Environmental Behavior of Organic Compounds. McGraw-Hill Book Co., New York. p. 4-9, 5-5.

Maazik, I.K. 1967. Standards for dimethylphenol isomers in water bodies. Gig. Sanit. 11: 28-35. (Russian with English translation)

Maazik, I.K. 1968. Dimethyl (xylenol) isomers and their standard contents in water reservoirs. Gig. Sanit. 33(9): 18-22. (Rus.) (CA 69:109642m)

Maazik, I.K. 1970. Toxicity of small dimethylphenol doses in chronic experiments. Vop. Gig. tr. Prof. Patol. Est. SSR. 9: 171-176. (Rus.) (CA 74:51747j)

Mabey, W.R., J.H. Smith, R.T. Podoll, et al. 1981. Aquatic Fate Process Data for Organic Priority Pollutants. Monitoring and Data Support Div., Office of Water Regulations and Standards, Washington, DC. EPA 440/4-81-014.

Miyamoto, J., K. Yamamoto and T. Matsumoto. 1969. Metabolism of 3,4-dimethylphenyl-N-methylcarbamate in white rats. Agric. Biol. Chem. 33(7): 1060-1073.

Pearce, P.J. and R.J.J. Simkins. 1968. Acid strengths of some substituted picric acids. Can. J. Chem. 46: 241-248.

Pool, B.L. and P.Z. Lin. 1982. Mutagenicity testing in the Salmonella typhimurium assay of phenolic compounds and phenolic fractions obtained from smokehouse smoke condensates. Food Chem. Toxicol. 20(4): 383-391.

Rogers, J.A. 1982. Solution thermodynamics of phenols. Int. J. Pharmaceut. 10: 89-97.

Southworth, G.R., S.E. Herbes, P.J. Franco and J.M. Giddings. 1985. Persistence of phenols in aquatic microcosms receiving chronic inputs of coal-derived oil. Water Air Soil Pollut. 24(3): 283-296.

Szybalksi, W. 1958. Special microbiological systems. 2. Observations on chemical mutagenesis in microorganisms. Ann. NY Acad. Sci. 76: 475-489.

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for 2,4-Dimethylphenol. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-044. NTIS PB81-117558.

U.S. EPA. 1980b. Guidelines and Methodology for the Preparation of Health Effect Assessment Chapters of the Consent Decree Water Criteria Documents. Federal Register. 45 (231): 79347-79357.

U.S. EPA. 1983. Methodology and Guidelines for Reportable Quantity Determinations Based on Chronic Toxicity Data. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1986. Guidelines for Carcinogen Risk Assessment. Federal Register. 51(185): 33992-34003.

Veldre, I.A. and H.J. Janes. 1979. Toxicological studies of shale oils, some of their components and commercial products. Environ. Health Perspect. 30: 141-146.

Visser, S.A., G. Lamontagne, V. Zoulalian and A. Tessier. 1977. Bacteria active in the degradation of phenols in polluted waters of the St. Lawrence River. Arch. Environ. Contam. Toxicol. 6(4): 455-469.

Weber, R.C., P.A. Parker and M. Bowser. 1981. Vapor pressure distribution of selected organic chemicals. U.S. EPA, Cincinnati, OH. 34 p. EPA 600/2-81-021.

Westall, J.C., C. Leuenberger and R.P. Schwarzenbach. 1985. Influence of pH and ionic strength on the aqueous-nonaqueous distribution of chlorinated phenols. Environ. Sci. Technol. 19(2): 193-198.

APPENDIX

Summary Table for 2,6-Dimethylphenol and 3,4-Dimethylphenol[a]

Oral	Isomer	Species/ Strain	Experimental Exposure/Dose (mg/kg/day)	Effect	Reference Dose (RfD_S or RfD)[b]
RfD_{SO}	2,6-	rat/albino	0.6 mg/kg/day 8 months	NOEL	0.42 mg/day
RfD_O	2,6-			NOEL	0.042 mg/day
Maximum CS	2,6-	rat/albino	6 mg/kg/day (RV_d=4.2)	weight loss, blood pressure increase, histopathological changes in liver, kidney and spleen (RV_e=5)	CS=21
RfD_{SO}	3,4-	rat/albino	1.4 mg/kg/day 8 months	NOEL	0.98 mg/day
RfD_O	3,4-			NOEL	0.098 mg/day
Maximum CS	3,4-	rat/albino	14 mg/kg/day (RV_d=3.7)	weight loss, blood pressure increase, histopathological changes in liver, kidney and spleen. (RV_e=5)	CS=18.5

[a]Source: Veldre and Janes, 1979

[b]mg/day for a 70 kg human. RfD_{SO} and RfD_O values are based on data for which complete details were not given; therefore, these values should only be used until more definitive studies are available.